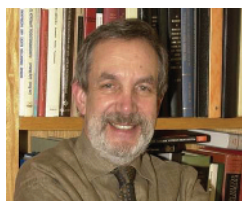


FEATURED EDITORIAL

Biological pacemaking: a concept whose time has come...or is coming

Michael R Rosen

"...when biological pacemakers reach clinical testing it is likely that some form of tandem therapy [with electronic pacemakers] will be used..."



The recognition of heart block is as old as recorded literature. In the 6th century BC Pien Ch'io wrote that "intermittency" of the pulse such that 1 of 50 beats was dropped did not indicate disease and was consistent with a normal life expectancy.¹ But dropping of 1 in 40 beats suggested a diseased organ (which organ is not stated) and a reduction in life expectancy to 4 years. Increasing numbers of dropped beats indicated more and more diseased organs and fewer years of life expectancy, and finally, when the dropped beats were 1 in 3–4, life was expected to end in 6–7 days.

Recognition is one thing; being able to provide treatment is another. When I was a medical student in the early 1960s the standard treatment for heart block was sublingual isoproterenol every two hours around the clock. Patients experienced catecholamine-induced arrhythmias; patients died of these or asystole—often within months. And in the 1960s, over two millennia after Pien Ch'io wrote of pulse intermittency, electronic pacing was just beginning to see extensive clinical application. The power packs—or cans—were bulky: implanted patients appeared to have hockey pucks under their clavicles.

ADVANCES IN PACING

How quickly the field of electronic pacing has advanced.² It has been one of the marvels of 20th century medicine. Cans are now miniaturised, atrioventricular-sequential pacing is commonplace, treatment of children—while still not easy—is at least possible in most instances, efforts are underway to make the units smarter in their situational rate responses, and units permitting pacing of previously inaccessible regions of the myocardium are now appearing.

Also appearing is the biological pacemaker, an experimental treatment not yet ready for patients.^{3–4} Investigators insert viral vectors encoding pacemaker genes into myocardial cells of animals in heart block,⁵ or use stem cells as platforms to deliver pacemaker genes native to⁶ or implanted in the stem cells⁷ to the recipient heart. Complementing this approach is the use of implanted cells to build atrioventricular bridges to carry impulses from atrium to ventricle in settings

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of experimentally-induced heart block and normal sinus node function.⁸

HOW DOES THE BIOLOGICAL PACEMAKER WORK?

Think of the basis of sinus node pacemaker function, which is a paradigm for all groups building biological pacemakers. The sinus node generates its pacemaker potential via the hyperpolarisation-induced opening of an ion channel of the HCN (hyperpolarisation-activated, cyclic nucleotide gated) family which has four isoforms, labelled HCN1–4.⁹ Membrane depolarisation occurs because of inward sodium current carried by this channel. Also contributing are the sodium–calcium exchanger and both T- and L-type calcium currents. The cell then repolarises because of outward current carried via potassium channels. In brief, any intervention that increases inward current and/or decreases outward current will increase pacemaker rate. Catecholamine binding to β -adrenergic receptors results in cyclic AMP binding to a site on the HCN channel, resulting in faster membrane depolarisation and increased rate; acetylcholine binding to muscarinic receptors has the opposite effect.

Initial attempts to build a biological pacemaker involved injecting plasmids encoding the β -2 adrenergic receptor into the atria of pigs and demonstrating faster heart rates in the presence and absence of catecholamine than occurred in control animals.¹⁰ The problem with this approach was the potential arrhythmogenicity of β -adrenergic agonists. The next step was the use of a dominant negative adenoviral construct to reduce expression of a potassium channel gene that hyperpolarised the membrane.¹¹ This was effective in the guinea pig but excessively prolonged repolarisation, a characteristic of potassium channel block that can cause proarrhythmia.¹²

HCN GENES

Our group and others have focused on the use of HCN genes^{5–13} or of potassium channel genes mutated to mimic certain characteristics of the HCN family.¹⁴ These are inserted via catheter injection into ventricles or atria of experimental animals to generate a variation on the pacemaker current I_f . The viral vectors result in episomal expression such that the overall duration of efficacy is unknown. Using this approach in proof of concept experiments, it has been shown that stable pacemaker function can ensue (although this is not always tested), and that the preparation of mutant or chimeric genes^{5–14–15} can importantly

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modify biological pacemaker rate. An additional approach used by our group is the loading of adult human mesenchymal stem cells with the HCN2 gene via electroporation (thereby avoiding viral vectors) and the injection of these cells into ventricular myocardium.⁷ The cells form gap junctions to deliver pacemaker current to adjacent myocytes and appear to be immunoprotected. These pacemakers remain functional for at least six weeks (the limit of time tested) without rejection.¹⁶

An alternative cell therapy involves the administration of human embryonic stem cells forced into a cardiogenic lineage which, when injected into the myocardium of pigs in heart block, generates a pacemaker current and couples effectively with myocardium to produce stable idioventricular rhythms.⁶ Issues here are the need for immunosuppressive therapy and the possibility of neoplastic transformation. The use of fetal and/or neonatal cell transplants is yet another experimental strategy.^{17–19}

While the above represents a great deal of work by several groups of investigators, much remains to be done. Issues of safety of viruses and of cell platforms must be understood, including their potential for migration to other sites in the body and the possibility that they might induce tumour formation.^{3,4} Their performance with respect to electronic units must be tested over time.^{3,4} This has led to the concept of tandem therapy, wherein a biological and an electronic pacemaker are implanted together⁵; the electronic unit provides a monitoring function for the biological unit as well as a backup should the biological unit fail. The biological unit provides autonomic responsiveness, and also is the major driver of the heart, thereby conserving the battery of the electronic unit. If and/or when biological pacemakers reach clinical testing it is likely that some form of tandem therapy will be used in the trials.

WHY DEVELOP BIOLOGICAL PACEMAKERS?

A question I am often asked is “Why...?” If electronic pacemakers are so good why do we and others expend the effort to build a biological unit? There are two parts to the answer. The first part is that as good as the electronic units are, they are still palliatives rather than cures: they have a finite life expectancy necessitating monitoring and maintenance, infection can still occur, they still confer problems on paediatric patients, and they are not as exquisitely responsive to the autonomic nervous system and the demands of exercise and emotion as our native sinus node.^{3,4} So there is room for something better.

The second part to the answer is more complex. We are in an era of runaway gene and cell therapy.^{20,21} The gene therapy is now on a shorter leash than was the case earlier, for two reasons: cures of the diseases being treated have been harder to come by than expected, and the viruses thought to be best suited for genomic incorporation of the genetic material delivered were associated with the development of cancer in unacceptably high percentages of patients studied. Cell therapy, whether involving the administration of human embryonic stem cells or of autologous or allogeneic adult stem cells, has not yet seen the necessary regulatory policies and safety issues addressed by government to ensure the uniform protection of human subjects on the receiving end of the therapy.^{20,21}

So we work on biological pacemakers because we want to get this treatment right: there is no emergency, patients will be well-protected for the most part by their electronic units, and

when the biological approach is ripe, it can begin to be used and the knowledge gained in getting it right can then be applied to other areas of gene and cell therapy. A final question I am asked is “How long will this take?” In the modern era it is fashionable to talk of making novel treatments available tomorrow. My response is, it will take as long as it has to; anything faster is irresponsible. But I expect it will be faster than the two-plus millennia between the report of Pien Ch’io¹ and the arrival of the electronic pacemaker.

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